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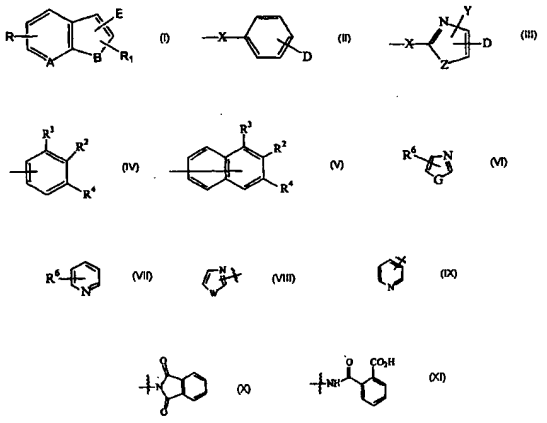
(54) Title: ARYLOXY-ACETIC ACID COMPOUNDS USEFUL AS INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)



(57) Abstract: This invention provides methods of inhibiting plasminogen activator inhibitory (PAI-1) in a mammal, utilizing compounds of the formula: (I) wherein: A is C or N; B is 0, S, N, or CH=CH; E is (II), (III), or -X-D; D is (IV), (V), or alkyl of 1-12 carbon atoms; X is CO, CH(OH), CH_2, or -CH-S-2-benzothiazole; Y is H, alkyl, or halo; Z is 0, S, or N; R is H, nitro, alkyl, alkoxy, halo, or CF_3; R^1 is alkyl, aryl, aralkyl, halo, Het-alkyl, or optionally substituted aryl; Het is (VI) or (VII); G is 0, S, or N; R^2 is H, halo, alkyl, or $-OR^5$; R^3 and R^4 are H, halo, alkyl, aryl, nitro, amino, alkylsulfoamide, arylsulfoamide, cycloalkyl, heterocycle, or optionally substituted aryl; R^5 is H, alkyl, $-CH(R^7)R^8$, $-C(CH_2)_nCO_2R^9$, $-C(CH_3)_2CO_2R^9$, $CH(R^7)(CH_2)_nCO_2R^9$, or $-CH(R^7)C_6H_4CO_2R^9$; R^6 is alkylene; R^7 is H, alkyl, aryl, aralkyl, cycloalkyl, phthalic acid, or Q-alkyl; Q is (VIII), (IX), (X), (XI); R^8 is $-CO_2R^{11}$, $-CONHR^{11}$, tetrazole, or $-PO_3R^{11}$; R^9 is H, alkyl, aryl, or aralkyl; W is 0, N, or S; R^{11} is H, alkyl, aryl, or aralkyl; n = 1-6; or a pharmaceutically acceptable salt or ester form thereof.

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ARYLOXY-ACETIC ACID COMPOUNDS USEFUL AS INHIBITORS OF PLASMINOGEN ACTIVATOR INHIBITOR-1 (PAI-1)

This invention relates to methods of using aryloxy-acetic acid derivatives as inhibitors of plasminogen activator inhibitor-1 (PAI-1) for treating conditions resulting from fibrinolytic disorders such as deep vein thrombosis and coronary heart disease, and pulmonary fibrosis, and to the use of such compounds in the manufacture of a medicament for the treatment of such conditions.

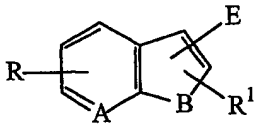
Background of Invention

Plasminogen activator inhibitor-1 (PAI-1) is a major regulatory component of the plasminogen-plasmin system. PAI-1 is the principal physiologic inhibitor of both tissue type plasminogen activator (t-PA) and urokinase type plasminogen activator (u-PA). Elevated plasma levels of PAI-1 have been associated with thrombotic events as indicated by animal experiments (Krishnamurti, *Blood,* 69, 798 (1987); Reilly, *Arteriosclerosis and Thrombosis*, 11, 1276 (1991); Carmeliet, *Journal of Clinical Investigation*, 92, 2756 (1993)) and clinical studies (Rocha, *Fibrinolysis*, 8, 294, 1994; Aznar, *Haemostasis* 24, 243 (1994)). Antibody neutralization of PAI-1 activity resulted in promotion of endogenous thrombolysis and reperfusion (Biemond, *Circulation*, 91, 1175 (1995); Levi, *Circulation* 85, 305, (1992)). Elevated levels of PAI-1 have also been implicated in diseases of women such as polycystic ovary syndrome (Nordt, *Journal of clinical Endocrinology and Metabolism*, 85, 4, 1563 (2000)) and bone loss induced by estrogen deficiency (Daci, *Journal of Bone and Mineral Research*, 15, 8, 1510 (2000)). Accordingly, agents that inhibit PAI-1 would be of utility in treating conditions originating from fibrinolytic disorder such as deep vein thrombosis, coronary heart disease, pulmonary fibrosis, polycystic ovary syndrome, etc.

U.S. Patent No. 6,110,963 teaches aryloxy acetic acid derivatives of this invention as useful in the treatment of hyperglycemia.

SUMMARY OF THE INVENTION

This invention comprises methods of inhibiting plasminogen activator inhibitor-1 (PAI-1) in a mammal, preferably in a human, the methods comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula:

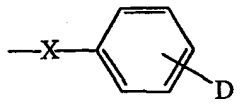
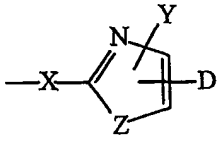


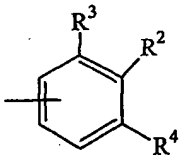
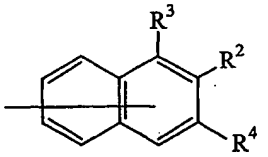
I

wherein

A is C or N;

B is O, S, N, or CH=CH;

E is  ,  , or -X-D ;

D is  ,  , or alkyl of 1-12 carbon atoms;

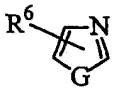
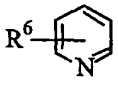
X is CO, CH(OH), CH_2, or -CH-S-2-benzothiazole;

Y is hydrogen, alkyl of 1-6 carbon atoms, or halogen;

Z is O, S, or N;

R is hydrogen, nitro, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^1 is alkyl of 1-12 carbon atoms, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, trifluoromethyl, and alkoxy of 1-6 carbon atoms ;

Het is  or  ;

G is O, S, or N;

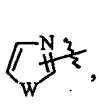
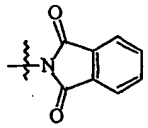
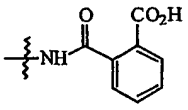
R^2 is hydrogen, halogen, alkyl of 1-6 carbon atoms, or $-OR^5$

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-8 carbon atoms, aryl of 6-12 carbon atoms, nitro, amino, alkylsulfoamide, arylsulfoamide, cycloalkyl of 3-8 carbon atoms, heterocycle of 5 to 7 ring atom containing from 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur, or aryl of 6-10 carbon atoms mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, trifluoromethyl, alkoxy of 1-6 carbon atoms;

R^5 is hydrogen, alkyl of 1-6 carbon atoms, $-CH(R^7)R^8$, $-C(CH_2)_nCO_2R^9$, $-C(CH_3)_2CO_2R^9$, $CH(R^7)(CH_2)_nCO_2R^9$, or $-CH(R^7)C_6H_4CO_2R^9$;

R^6 is alkyl of 1-3 carbon atoms;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, aralkyl of 6-12 carbon atoms, cycloalkyl of 3-8 carbon atoms, phthalic acid, or Q-alkyl wherein the alkyl moiety contains 1-6 carbon atoms;

Q is  ,  ,  , or  ;

R^8 is $-CO_2R^{11}$, $-CONHR^{11}$, tetrazole, or $-PO_3R^{11}$;

R^9 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, or aralkyl of 7-15 carbon atoms;

W is O, N, or S;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, or aralkyl of 7-15 carbon atoms;

n = 1-6;

or a pharmaceutically acceptable salt or ester form thereof.

Alkyl, as used herein refers to an aliphatic hydrocarbon chain and includes straight and branched chains e.g. of 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neo-pentyl, n-hexyl, and isohexyl. Halogen means bromine, chlorine, fluorine, and iodine. It is preferred that the aryl portion of the aryl or aralkyl substituents herein is a phenyl, naphthyl or 1,4-benzodioxan-5-yl group; with phenyl being most preferred. The aryl moiety may be optionally mono-, di-, or tri- substituted with a substituent selected from the group consisting of alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, trifluoromethyl, halogen, alkoxycarbonyl of 2-7 carbon atoms, alkylamino of 1-6 carbon atoms, and dialkylamino in which each of the alkyl groups is of 1-6 carbon atoms, nitro, cyano, $-CO_2H$, alkylcarbonyloxy of 2-7 carbon atoms, and alkylcarbonyl of 2-7 carbon atoms.

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The compounds of the present invention are inhibitors of the serine protease inhibitor PAI-1, and are therefore useful in the treatment, inhibition, prevention or prophylaxis in a mammal, preferably in a human, of those processes which involve the production and/or action of PAI-1. Thus, the compounds of the invention are useful in the treatment or prevention of noninsulin dependent diabetes mellitus cardiovascular disease caused by such condition, and and prevention of thrombotic events associated with coronary artery and cerebrovascular disease. These compounds are also useful for inhibiting the disease process involving the thrombotic and prothrombotic states which include, but are not limited to, formation of atherosclerotic plaques, venous and arterial thrombosis, myocardial ischemia, atrial fibrillation, deep vein thrombosis, coagulation syndromes, pulmonary fibrosis, cerebral thrombosis, thromboembolic complications of surgery (such as joint

replacement), and peripheral arterial occlusion. These compounds are also useful in treating stroke associated with or resulting from atrial fibrillation.

The compounds of the invention may also be used in the treatment of diseases associated with extracellular matrix accumulation, including, but not limited to, renal fibrosis, chronic obstructive pulmonary disease, polycystic ovary syndrome, restenosis, renovascular disease and organ transplant rejection.

The compounds of the invention may also be useful in the treatment of malignancies, and diseases associated with neoangiogenesis (such as diabetic retinopathy).

The compounds in the invention may also be used in conjunction with and following processes or procedures involving maintaining blood vessel patency, including vascular surgery, vascular graft and stent patency, organ, tissue and cell implantation and transplantation. The compounds in the invention may also be useful in the treatment of inflammatory diseases, septic shock and the vascular damage associated with infections.

The compounds of the invention are useful for the treatment of blood and blood products used in dialysis, blood storage in the fluid phase, especially *ex vivo* platelet aggregation. The present compounds may also be added to human plasma during the analysis of blood chemistry in hospital settings to determine the fibrinolytic capacity thereof.

The compounds in the present invention may also be used in combination with prothrombolytic , fibrinolytic and anticoagulant agents.

The compounds of the present invention may also be used to treat cancer including, but not limited to, breast and ovarian cancer, and as imaging agents for the identification of metastatic cancers.

The compounds of the invention may also be used in the treatment of Alzheimer's disease. This method may also be characterized as the inhibition of plasminogen activator by PAI-1 in a mammal, particularly a human, experiencing or subject to Alzheimer's disease. This method may also be characterized as a method

of increasing or normalizing levels of plasmin concentration in a mammal, particularly those experiencing or subject to Alzheimer's disease.

The compounds of the invention may be used for the treatment of myelofibrosis with myeloid metaplasia by regulating stromal cell hyperplasia and increases in extracellular matrix proteins.

The compounds of the invention may also be used in conjunction with protease inhibitor-containing highly active antiretroviral therapy (HAART) for the treatment of diseases which orginate from fibrinolytic impairment and hypercoagulability of HIV-1 infected patients receiving such therapy.

The compounds of the invention may be used for the treatment of diabetic nephropathy and renal dialysis associated with nephropathy.

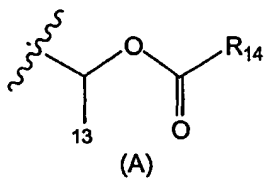
The compounds of the invention may be used to treat cancer, septicemia, obesity, insulin resistance, proliferative diseases such as psoriasis, improving coagulation homeostasis, cerebrovascular diseases, microvascular disease, hypertension, dementia, osteoporosis, arthritis, asthma, heart failure, arrhythmia, angina, and as a hormone replacement agent, treating, preventing or reversing progression of atherosclerosis, Alzheimer's disease, osteoporosis, osteopenia; reducing inflammatory markers, reducing C-reactive protein, or preventing or treating low grade vascular inflammation, stroke, dementia, coronary heart disease, primary and secondary prevention of myocardial infarction, stable and unstable angina, primary prevention of coronary events, secondary prevention of cardiovascular events, peripheral vascular disease, peripheral arterial disease, acute vascular syndromes, reducing the risk of undergoing a myocardial revascularization procedure, microvascular diseases such as nephropathy, neuropathy, retinopathy and nephrotic syndrome, hypertension, Type I and 2 diabetes and related diseases, hyperglycemia, hyperinsulinemia, malignant lesions, premalignant lesions, gastrointestinal malignancies, liposarcomas and epithelial tumors, proliferative diseases such as psoriasis, improving coagulation homeostasis, and/or improving endothelial function, and all forms of cerebrovascular diseases.

The compounds of the invention may be used for the topical applications in wound healing for prevention of scarring.

This invention also comprises methods for the treatment, inhibition, prevention or prophylaxis in a mammal of each of the conditions or maladies listed herein. Each method comprises administering to a mammal in need thereof a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt or ester form thereof.

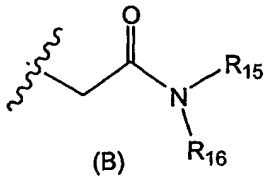
Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, napthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, preferably alkali metal salts, for example, sodium, lithium, or potassium, when a compound of this invention contains a carboxylate or phenolic moiety, or similar moiety capable of forming base addition salts.

Ester forms of the compounds of this invention include straight chain alkyl esters having from 1 to 6 carbon atoms or branched chain alkyl groups containing 3 or 6 carbon atoms, including methyl, ethyl, propyl, butyl, 2-methylpropyl and 1,1-dimethylethyl esters. Other esters useful with this invention include those of the formula $-COOR_{12}$ wherein R_{12} is selected from the formulae:



(A)

or



(B)

wherein R_{13}, R_{14}, R_{15}, and R_{16}, are independently selected from hydrogen, alkyl of from 1 to 10 carbon atoms, aryl of 6 to 12 carbon atoms, arylalkyl of from 6 to 12

carbon atoms; heteroaryl or alkylheteroaryl wherein the heteroaryl ring is bound by an alkyl chain of from 1 to 6 carbon atoms.

Among the preferred ester forms of the compounds herein include but not limited to C_1-C_6 alkyl esters, C_3-C_6 branched alkyl esters, benzyl esters, etc.

Preferably, A is C.

Preferably, R is hydrogen.

Preferably, R^1 is hydrogen, alkyl of 1-6 carbon atoms, or aralkyl of 7-15 carbon atoms.

Preferably, R^3 and R^4 are each, independently, hydrogen or halogen.

Among the preferred compounds of this invention are those of Formula I, in which:
A is C;
R is hydrogen;
R^1 is hydrogen, alkyl of 1-6 carbon atoms, or aralkyl of 7-15 carbon atoms; and
R^3 and R^4 are each, independently, hydrogen or halogen;
or a pharmaceutically acceptable salt thereof.

Specifically preferred compounds for use in the methods of the present invention include those set forth below:

6-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl-naphthalen-2-ol;

6-[(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-ol;

1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-ol;

[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxy]-acetic acid;

2-[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxy]-3-phenyl-propionic acid;

5-[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxymethyl]-1H-tetrazole;

6-(2-butyl-benzofuran-3-ylmethyl)-1-iodo-naphthalen-2-ol;

2-[-6-(2-butyl-benzofuran-3-ylmethyl)-1-iodo-naphthalen-2-yloxy]-3-phenyl-propionic acid;

1-bromo-6-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-naphthalen-2-ol;

[1-bromo-6-(2-butyl-benzofuran-3-carbonyl)-naphthalen-2-yloxy]-acetic acid;

2-[1-bromo-6-(2-butyl-benzofuran-3-carbonyl)-naphthalen-2-yloxy] -3-phenyl-propionic acid;

[5-bromo-6-(1H-tetrazol-5-ylmethoxy)-naphthalen-2-yl]-(2-butyl-benzofuran-3-yl)-methanone;

6-(2-benzyl-benzo[b]thiophen-3-ylmethyl)-1-bromo-naphthalen-2-ol;

4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-ol;

(2-butyl-benzofuran-3-yl)-(4'-hydroxy-biphenyl-4-yl)-methanone;

4'-[(2-butyl-benzofuran-3-ylmethyl]-biphenyl-4-ol;

[4'-[(2-butyl-benzofuran-3-ylmethyl]-biphenyl-4-yloxy]-acetic acid;

5-[4'-(2-butyl-benzofuran-3-ylmethyl) -biphenyl-4-yloxymethyl]-1H-tetrazole;

{4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-yloxy}-acetic acid;

3,5-dibromo-4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-ol;

4'-[(2-benzyl-benzo[b]thiophen-3-yl)-hydroxy-methyl]-biphenyl-4-ol;

(2-butyl-benzofuran-3-yl)-[5-(4-methoxy-phenyl)-oxazol-2-yl]-methanol;

(2-butyl-benzofuran-3-yl)-[5-(4-methoxy-phenyl)-oxazol-2-yl]-methanone;

2-(2-butyl-benzofuran-3-ymethyl)-5-(4-methoxy-phenyl)-oxazole;

[4-bromo-5-(4-methoxy-phenyl)-oxazol-2-yl]-(2-butyl-benzofuran-3-yl)-methanone;

4-bromo-5-(6-bromo-2-butyl-benzofuran-3-ylmethyl)-5-(4-methoxy-phenyl)-oxazole;

6-[(benzothiazol-2-ylsulfanyl)-(2-butyl-benzofuran-3-yl)-methyl]-naphthalen-2-ol;

4'-[(2-butyl-benzofuran-3-yl)-(benzothiazol-2-ylsulfanyl)-methyl]-biphenyl-4-ol;

2-[1-(benzo[b]thiophen-2-yl)-octylsulfanyl]-benzothiazole;

2-[(4-bromo-phenyl)-(2-butyl-benzofuran-3-yl)-methylsulfanyl]-benzothiazole;

2-[(4-bromo-naphthalen-1-yl)-(2-butyl-benzofuran-3-yl)-methylsulfanyl]-benzothiazole;

2-[(2-butyl-benzofuran-3-yl)-phenyl-methylsulfanyl]-benzothiazole;

[2,6-dibromo-4-(naphthalene-2-carbonyl)-phenoxy]-acetic acid;

5-[2,6-dibromo-4-(naphthalen-2-ylmethyl)-phenoxymethyl]-1H-tetrazole;

or a pharmaceutically acceptable salt or ester form thereof.

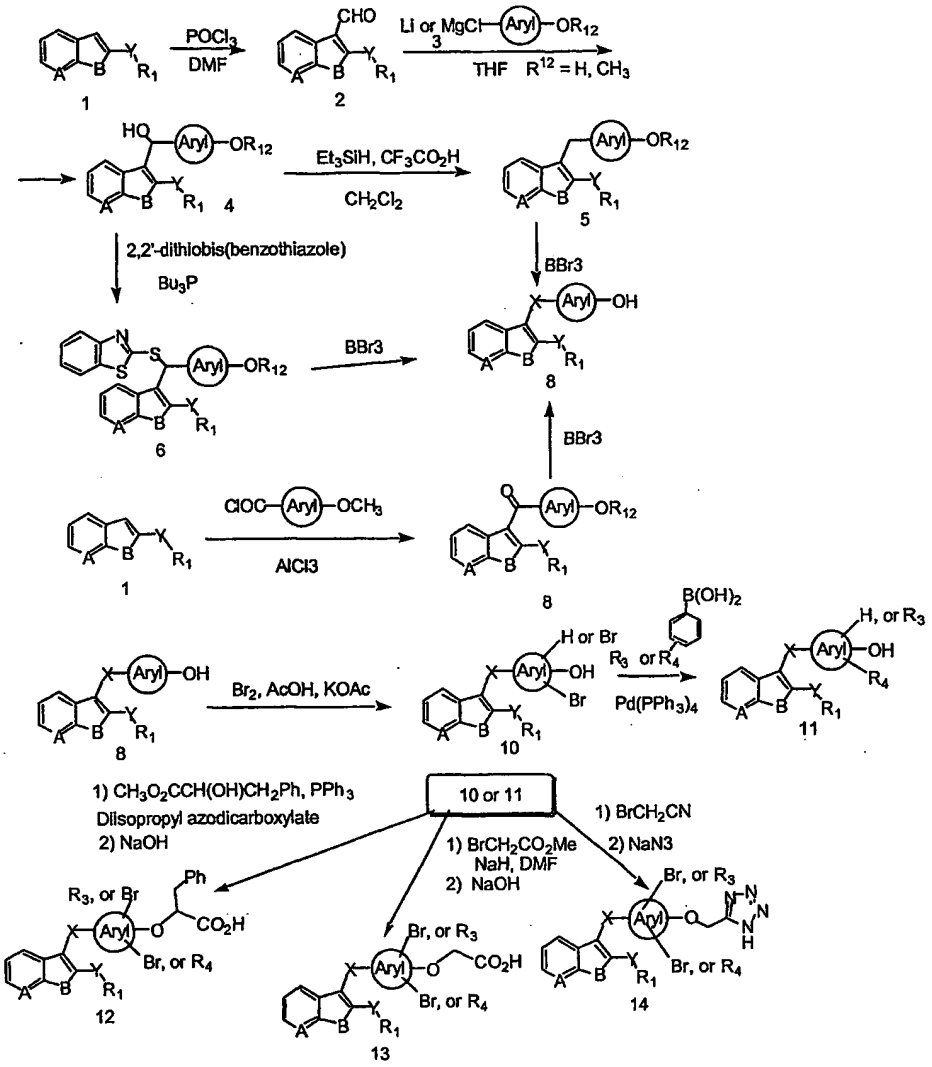
The invention also relates to the use of compounds of the invention in the preparation of a medicament for inhibiting plasminogen activator inhibitor-1 (PAI-1) in a mammal.

The invention also relates to the use of compounds of the invention in the preparation of a medicament for the treatment of thrombosis or fibrinolytic impairment in a mammal.

The compounds of this invention can be prepared as described in U.S. Patent No. 6,110,963 (Malamas et al.- issued August 29, 2000), the contents of which are incorporated herein by reference, or by other methods known in the art.

The compounds of this invention can be prepared according to the following schemes from commercially available starting materials or starting materials which can be prepared using to literature procedures. These schemes show the preparation of representative compounds of this invention.

Scheme I



In Scheme I compounds (1) that are either commercially available or can be prepared by known methodologies from the 2-lithiated derivatives, obtained by treatment with alkyllithium reagents, of compounds (1) and the appropriate electrophiles Y-R^1 [ref. Org. React. 1979, volue 26]. Compounds (1) can be converted to 3-carboxaldehydes (2) upon treatment with phosphorus oxychloride and

N,N-dimethylformamide [ref. Chim. Ther. 1996, 4, 221-227]. Aldehydes (2) can be treated with aromatic or heteroaromatic lithium (prepared by lithium halogen exchange, using for example n-BuLi) or Grignard reagents (3) to afford methyl-alcohols (4). Alcohols (4) can be reduced with triethylsilane/trifluoroacetic acid to produce (5) or can be converted to benzothiazoles (6) upon reaction with 2,2-dithiobis(benzothiazole) and tributylphosphine. Compounds (1) can also be converted to ketones (7) upon treatment with acyl chlorides and aluminum chloride [Friedel-Crafts and Related Reactions, Wiley Interscience, New York, 1963-1965]. Compounds (5), (6), and (7) can produce phenols (8) upon treatment with boron tribromide. Compounds (8) can be monobrominated or dibrominated (10) with bromine in the presence of potassium acetate and acetic acid. The brominated compounds (10) can be converted to terphenyl analogs (11) using the Suzuki protocol (arylboronic acids / palladium catalyst) [ref. Syn. Comm. 1981, 11, 513-519]. Compounds (10) and (11) can be treated with bromoacetonitile in the presence of sodium hydride to give oxo-nitriles that can subsequently be converted to tetrazoles (14) upon treatment with sodium azide and ammonium chloride. Secondly, compounds (10) and (11) can be converted to the oxo-acetic acids (13) upon treatment with methyl bromoacetate, followed by saponification with sodium hydroxide. Thirdly, compounds (10) and (11) can be converted to carboxylic acids (12) by using the Mitsunobu protocol [ref. *Synthesis.* 1981, 1-27], for example, phenyllactic acid methyl ester, triphenylphosphine and diisopropyl azodicarboxylate. Conversion of either (10) or (11) to (12), (13) or (14) when X is -CH(OH)- will require the masking of the hydroxyl group, for examle with a silyl reagent, followed by unmasking at the last step, for example with tetrabutylammonium fluoride.

The precise dosage to be employed depends upon several factors including the host, whether in veterinary medicine or human medicine, the nature and severity of the condition being treated, the mode of administration and the particular active substance employed. The compounds may be administered by any conventional route, in particular enterally, preferably orally in the form of tablets or capsules. Administered compounds can be in the free form or pharmaceutically acceptable salt form as appropriate, for use as a pharmaceutical, particularly for use in the prophylactic or curative treatment of atherosclerosis and sequelae (angina pectoris,

myocardial infarction, arrhythmias, heart failure, kidney failure, stroke, peripheral arterial occlusion, and related disease states). These measures will slow the rate of progress of the disease state and assist the body in reversing the process direction in a natural manner.

Effective administration of these compounds may be given at a daily dosage of from about 1 mg/kg to about 250 mg/kg, and may given in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parenterally (including intravenous, intraperitoneal and subcutaneous injections), rectally, vaginally, and transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

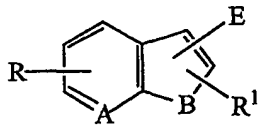
Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter

the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgment of the medical practitioner involved. It is preferred that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

CLAIMS:

1. A method of inhibiting plasminogen activator inhibitor-1 (PAI-1) in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula:

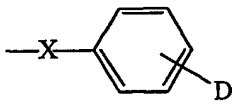
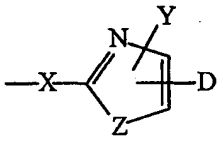


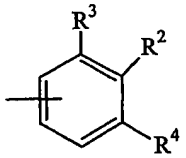
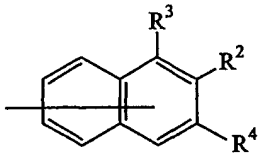
I

wherein

A is C or N;

B is O, S, N, or CH=CH;

E is  ,  , or -X-D ;

D is  ,  , or alkyl of 1-12 carbon atoms;

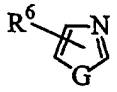
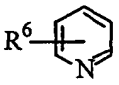
X is CO, CH(OH), CH_2, or -CH-S-2-benzothiazole;

Y is hydrogen, alkyl of 1-6 carbon atoms, or halogen;

Z is O, S, or N;

R is hydrogen, nitro, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, or trifluoromethyl;

R^1 is alkyl of 1-12 carbon atoms, aryl of 6-10 carbon atoms, aralkyl of 7-15 carbon atoms, halogen, Het-alkyl wherein the alkyl moiety contains 1-6 carbon atoms, or aryl mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, trifluoromethyl, and alkoxy of 1-6 carbon atoms ;

Het is  or  ;

G is O, S, or N;

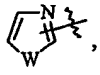
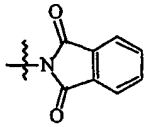
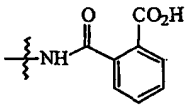
R^2 is hydrogen, halogen, alkyl of 1-6 carbon atoms, or $-OR^5$

R^3 and R^4 are each, independently, hydrogen, halogen, alkyl of 1-8 carbon atoms, aryl of 6-12 carbon atoms, nitro, amino, alkylsulfoamide, arylsulfoamide, cycloalkyl of 3-8 carbon atoms, heterocycle of 5 to 7 ring atom containing from 1 to 3 heteroatoms selected from oxygen, nitrogen, or sulfur, or aryl of 6-10 carbon atoms mono-, di- or tri-substituted with a substituent selected from the group consisting of halogen, alkyl of 1-6 carbon atoms, trifluoromethyl, alkoxy of 1-6 carbon atoms;

R^5 is hydrogen, alkyl of 1-6 carbon atoms, $-CH(R^7)R^8$, $-C(CH_2)_nCO_2R^9$, $-C(CH_3)_2CO_2R^9$, $CH(R^7)(CH_2)_nCO_2R^9$, or $-CH(R^7)C_6H_4CO_2R^9$;

R^6 is alkyl of 1-3 carbon atoms;

R^7 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, aralkyl of 6-12 carbon atoms, cycloalkyl of 3-8 carbon atoms, phthalic acid, or Q-alkyl wherein the alkyl moiety contains 1-6 carbon atoms;

Q is  ,  ,  , or  ;

R^8 is $-CO_2R^{11}$, $-CONHR^{11}$, tetrazole, or $-PO_3R^{11}$;

R^9 is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, or aralkyl of 7-15 carbon atoms;

W is O, N, or S;

R^{11} is hydrogen, alkyl of 1-6 carbon atoms, aryl of 6-12 carbon atoms, or aralkyl of 7-15 carbon atoms;

n = 1-6;

or a pharmaceutically acceptable salt or ester form thereof.

2. A method according to Claim 1 wherein A is C.

3. A method according to Claim 1 or 2 wherein R is hydrogen.

4. A method according to any one of Claims 1 to 3 wherein R^1 is hydrogen, alkyl of 1-6 carbon atoms, or aralkyl of 7-15 carbon atoms.

5. A method according to any one of Claims 1 to 4 wherein R^3 and R^4 are each, independently, hydrogen or halogen.

6. A method according to Claim 1 wherein
A is C;
R is hydrogen;
R^1 is hydrogen, alkyl of 1-6 carbon atoms, or aralkyl of 7-15 carbon atoms; and
R^3 and R^4 are each, independently, hydrogen or halogen;
or a pharmaceutically acceptable salt thereof.

7. A method according to Claim 1 wherein the compound is selected from the group of:
6-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl-naphthalen-2-ol;
6-[(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-ol;
1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-ol;
[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxy]-acetic acid; or
2-[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxy]-3-phenyl-propionic acid;
or a pharmaceutically acceptable salt or ester form thereof.

8. A method according to Claim 1 wherein the compound is selected from the group of:
5-[1-bromo-6-(2-butyl-benzofuran-3-ylmethyl)-naphthalen-2-yloxymethyl]-1H-tetrazole;
6-(2-butyl-benzofuran-3-ylmethyl)-1-iodo-naphthalen-2-ol;

2-[-6-(2-butyl-benzofuran-3-ylmethyl)-1-iodo-naphthalen-2-yloxy]-3-phenyl-propionic acid;
1-bromo-6-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-naphthalen-2-ol;
[1-bromo-6-(2-butyl-benzofuran-3-carbonyl)-naphthalen-2-yloxy]-acetic acid;
or a pharmaceutically acceptable salt or ester form thereof.

9. A method according to Claim 1 wherein the compound is selected from the group of:
2-[1-bromo-6-(2-butyl-benzofuran-3-carbonyl)-naphthalen-2-yloxy] -3-phenyl-propionic acid;
[5-bromo-6-(1H-tetrazol-5-ylmethoxy)-naphthalen-2-yl]-(2-butyl-benzofuran-3-yl)-methanone;
6-(2-benzyl-benzo[b]thiophen-3-ylmethyl)-1-bromo-naphthalen-2-ol;
4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-ol; or
(2-butyl-benzofuran-3-yl)-(4'-hydroxy-biphenyl-4-yl)-methanone;
or a pharmaceutically acceptable salt or ester form thereof.

10. A method according to Claim 1 wherein the compound is selected from the group of:
4'-[(2-butyl-benzofuran-3-ylmethyl]-biphenyl-4-ol;
[4'-[(2-butyl-benzofuran-3-ylmethyl]-biphenyl-4-yloxy]-acetic acid;
5-[4'-(2-butyl-benzofuran-3-ylmethyl) -biphenyl-4-yloxymethyl]-1H-tetrazole;
{4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-yloxy}-acetic acid;
3,5-dibromo-4'-[(2-butyl-benzofuran-3-yl)-hydroxy-methyl]-biphenyl-4-ol; or
4'-[(2-benzyl-benzo[b]thiophen-3-yl)-hydroxy-methyl]-biphenyl-4-ol;
or a pharmaceutically acceptable salt or ester form thereof.

11. A method according to Claim 1 wherein the compound is selected from the group of:
(2-butyl-benzofuran-3-yl)-[5-(4-methoxy-phenyl)-oxazol-2-yl]-methanol;
(2-butyl-benzofuran-3-yl)-[5-(4-methoxy-phenyl)-oxazol-2-yl]-methanone;
2-(2-butyl-benzofuran-3-ymethyl)-5-(4-methoxy-phenyl)-oxazole;
[4-bromo-5-(4-methoxy-phenyl)-oxazol-2-yl]-(2-butyl-benzofuran-3-yl)-methanone; or

4-bromo-5-(6-bromo-2-butyl-benzofuran-3-ylmethyl)-5-(4-methoxy-phenyl)-oxazole;
or a pharmaceutically acceptable salt or ester form thereof.

12. A method according to Claim 1 wherein the compound is selected from the group of:
6-[(benzothiazol-2-ylsulfanyl)-(2-butyl-benzofuran-3-yl)-methyl]-naphthalen-2-ol;
4'-[(2-butyl-benzofuran-3-yl)-(benzothiazol-2-ylsulfanyl)-methyl]-biphenyl-4-ol;
2-[1-(benzo[b]thiophen-2-yl)-octylsulfanyl]-benzothiazole;
2-[(4-bromo-phenyl)-(2-butyl-benzofuran-3-yl)-methylsulfanyl]-benzothiazole; or
2-[(4-bromo-naphthalen-1-yl)-(2-butyl-benzofuran-3-yl)-methylsulfanyl]-benzothiazole;
or a pharmaceutically acceptable salt or ester form thereof.

13. A method according to Claim 1 wherein the compound is selected from the group of:
2-[(2-butyl-benzofuran-3-yl)-phenyl-methylsulfanyl]-benzothiazole;
[2,6-dibromo-4-(naphthalene-2-carbonyl)-phenoxy]-acetic acid; or
5-[2,6-dibromo-4-(naphthalen-2-ylmethyl)-phenoxymethyl]-1H-tetrazole;
or a pharmaceutically acceptable salt or ester form thereof.

14. A method for treatment of thrombosis or fibrinolytic impairment in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt or ester form thereof.

15. A method according to Claim 14 wherein the thrombosis or fibrinolytic impairment is associated with formation of atherosclerotic plaques, venous and arterial thrombosis, myocardial ischemia, atrial fibrillation, deep vein thrombosis, coagulation syndromes, pulmonary fibrosis, cerebral thrombosis, thromboembolic complications of surgery or peripheral arterial occlusion.

16. Use of a compound of formula (I) as defined in Claims 1 to 13 in the preparation of a medicament for inhibiting plasminogen activator inhibitor (PAI-1) in a mammal.

17. Use of a compound of formula (I) as defined in Claims 1 to 13 in the preparation of a medicament for the treatment of thrombosis or fibrinolytic impairment in a mammal.

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/US 02/19240

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/425 A61K31/42 A61K31/41 A61K31/38 A61K31/34 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, BIOSIS, PASCAL, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHARLTON, PETER: "The status of plasminogen activator inhibitor-1 as a therapeutic target" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 6, no. 5, pages 539-554, XP009000012 page 542, column 1, paragraph 1 -page 545, column 2, paragraph 1 ---	1-17
A	MALAMAS, MICHAEL S. ET AL: "Novel Benzofuran and Benzothiophene Biphenyls as Inhibitors of Protein Tyrosine Phosphatase 1B with Antihyperglycemic Properties" JOURNAL OF MEDICINAL CHEMISTRY (2000), 43(7), 1293-1310 , XP002216395 -----	

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2002	31/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Friederich, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.....national application No.
PCT/US 02/19240

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 14 and 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 1-13 and 16 relate to compounds defined (inter alia) by reference to their PAI-1 antagonistic activity.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the parts relating to the diseases mentioned in the description at page 4, line 22 - page 7, line 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.